Original Article

Respiratory Factors Contributing to Exercise Intolerance in Breast Cancer Survivors: A Case-Control Study

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Abstract

Context. Breast cancer survivors often experience activity-related dyspnea and exercise intolerance, but the underlying mechanisms remain unknown.

Objectives. We evaluated physiological contributors to reduced peak oxygen uptake (VO_2), with particular attention to the role of respiratory impairment.

Methods. We compared symptom assessments, respiratory and peripheral muscle strength, pulmonary function, and ventilatory responses to symptom-limited incremental treadmill exercise in 29 women who had survived breast cancer and 29 age-matched healthy controls.

Results. Peak VO_2 was reduced more than 20%, on average, in the cancer group compared with controls ($P < 0.001$). Slopes of dyspnea intensity ratings over ventilation or VO_2 were >50% greater in the cancer group compared to controls ($P < 0.05$). Women with breast cancer had lower lung diffusing capacity for carbon monoxide (D_LCO), respiratory and limb muscle strength, and ventilatory thresholds during exercise compared with controls (all $P < 0.05$). During exercise, indices of ventilatory efficiency were similar to controls, but inspiratory capacity (IC) was lower and breathing pattern was more rapid and shallow in the cancer group ($P < 0.05$). The lower peak VO_2 in the cancer group was associated with greater dyspnea intensity, and lower D_LCO, IC and ventilatory threshold (all $P < 0.05$).

Conclusion. Breast cancer survivors had greater peripheral and respiratory muscle weakness, greater reduction of IC, impaired lung diffusion, and evidence of deconditioning compared with controls. Exercise intolerance was multifactorial and correlated well with the combination of these factors as well as with exertional dyspnea. Individualized physiological testing in breast cancer survivors can identify important contributors to exercise intolerance which can be targeted for treatment. J Pain Symptom Manage 2016;■:■–■.

Key Words

Breast cancer, dyspnea, muscle weakness, exercise, cardiopulmonary exercise test

Introduction

The number of breast cancer survivors continues to increase as a result of population aging and advances in modern cancer treatment.[1] There is abundant evidence that women successfully treated for breast cancer can have ongoing morbidity with symptoms of dyspnea, exercise intolerance (reduced exercise capacity as measured by peak oxygen consumption [VO_2]), and reduced physical activity that can result in perceived poor health status.[2–6] Effective amelioration of the common symptoms of dyspnea and exercise intolerance awaits a better understanding of their underlying physiological mechanisms.

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Previously, we have advocated the use of detailed physiological testing, including cardiopulmonary exercise testing, to uncover contributory factors to unexplained or disproportionate dyspnea in individuals with various cancers.[6] In breast cancer patients who are clinically stable and remote from treatment interventions, potential contributors to dyspnea and exercise intolerance include the effects of the underlying cancer, the adverse effects of chemotherapy and/or radiotherapy, and the effects of deconditioning due to inactivity.[2–17] Indeed, the mechanisms are likely multifactorial and may include 1) increased ventilatory demand secondary to ventilation-perfusion abnormalities[7,8]; 2) decreased ventilatory capacity secondary to inspiratory muscle weakness[6,9,10]; 3) impaired dynamic respiratory mechanics secondary to peripheral airway dysfunction or lung restriction[6–8,11–15]; 4) impairment of lung diffusing capacity secondary to microvascular injury[6–8,12–15]; 5) cardiocirculatory impairment[16,17]; or 6) any combination of the above. Several studies have highlighted the importance of deconditioning and reduced cardiorespiratory fitness in breast cancer survivors, but the role of respiratory impairment per se remains unknown.[2–5,16]

The present study extends the previous work by examining specific respiratory-related contributions to exercise intolerance in women treated for breast cancer. Based on previous studies in various cancer groups,[6,9] we postulated that exertional dyspnea and exercise intolerance in breast cancer survivors would be associated, not only with increased ventilatory demand secondary to deconditioning, but also with reduced inspiratory capacity (IC) and inspiratory muscle weakness. To test this hypothesis, we selected clinically stable women with breast cancer who did not have overt cardiorespiratory disease or other comorbidities that could contribute to exercise intolerance. We compared physiological parameters collected at rest and during incremental exercise in the cancer patients and age-matched healthy controls. Finally, we examined interrelationships between exercise capacity, dyspnea intensity ratings, and pertinent physiological markers which included measures of IC, respiratory muscle strength, and ventilatory efficiency during exercise.

Methods

This cross-sectional study analyzed a subset of data collected in a larger sample of outpatients with cancer and healthy controls who performed physiological testing in our laboratory. There is no overlap between the current analysis and that of the original study which examined mechanisms of unexplained dyspnea in a variety of cancer types: a portion of the larger sample of data has been previously published along with a detailed methodology.[6] Of 129 subjects tested, 30 were identified as women with breast cancer, one of whom did not meet study eligibility criteria (see the following) because of abnormal baseline spirometry. Thus, 29 women with breast cancer and 29 age-matched healthy women were included in this analysis. Subjects provided written informed consent as part of the original study. The Queen's University Health Sciences & Affiliated Hospitals Research Ethics Board approved the current analysis and waived the need for additional informed consent (DMED-1676-14).

Subjects

Adult women with breast cancer were included if they had stable disease, a life expectancy more than three months, and no chemotherapy or radiotherapy in the previous three months (to allow time for recovery and ensure clinical stability). Exclusion criteria were as follows: 1) dyspnea that could be attributed to known cardiopulmonary disease, whether cancer-related or coexisting; 2) primary or secondary lung cancer, chronic obstructive pulmonary disease, asthma, ischemic heart disease, congestive heart failure, or significant cardiac arrhythmias; 3) abnormal resting spirometry (forced expiratory volume in one second [FEV_1] <80% predicted, forced vital capacity [FVC] <80% predicted, or $FEV_1/FVC<0.7$); 4) abnormal chest radiograph; 5) resting oxygen saturation (SpO_2) <90%; or 6) hemoglobin concentration <100 g/L. Age-matched healthy women were recruited by advertising in the community.

Procedures

Height, weight, waist and hip circumferences, and skinfold thicknesses were measured.[18] Blood from the cancer group was analyzed for complete blood count, hemoglobin, albumin, and electrolyte concentrations. Chronic activity-related dyspnea was assessed using the Baseline Dyspnea Index and modified Medical Research Council dyspnea scale: Baseline Dyspnea Index total scores range from 0 (most severe dyspnea) to 12 (no dyspnea) and the modified Medical Research Council dyspnea scale ranges from 0 (best) to 4 (worst).[19,20] Habitual physical activity was assessed as either "active" (exercised regularly at least twice per week) or "sedentary."

Spirometry, body plethysmography, diffusing capacity of the lung for carbon monoxide (D_LCO), and maximal inspiratory and expiratory mouth pressures (MIP, MEP) were measured (Vmax 229d and Autobox 6200 D_L; SensorMedics, Yorba Linda, CA) according to recommended standards.[21–24] Measurements were expressed relative to predicted normal values.[25–31]

Symptom-limited incremental cardiopulmonary exercise tests were performed on a treadmill (Medtrack ST55 with Q710; Quinton Instrument Co., Bothell, WA) using SensorMedics Vmax 229d testing equipment as previously described.[6] In addition to breath-by-breath measurements, assessments included SpO_2 by pulse oximetry; heart rate (HR) by electrocardiography; blood pressure by auscultation; serial IC measurements for evaluation of operating lung volumes[32]; and intensity of perceived breathing and leg discomfort rated with the modified 10-point Borg scale.[33] Data were averaged in 30-second intervals throughout the test, and "peak exercise" data were averaged over the last 30 seconds of exercise. Peak VO_2 was compared with predicted normal values accounting for sex, age, height, and weight; a 9% correction factor was applied to estimate the difference between treadmill and cycle testing.[34] Ventilatory (anaerobic) thresholds were determined by combining three methods.[35] Relationships between tidal volume (V_T) and minute ventilation (V_E) were examined, and the inflection point was determined for each subject to represent the onset of mechanical constraints on V_T expansion.[36] Expiratory flow limitation was crudely assessed by comparing the overlap of tidal flow-volume loops with the maximal flow-volume loop.[37] Maximum ventilatory capacity was estimated as $35 \times FEV_1$.[38]

Leg (knee) and arm (elbow) strength were measured using a computerized isokinetic dynamometer (Cybex International, Medway, MA). Peak torque was averaged from four maximal flexion/extension efforts made for each joint at a 90°/s angular velocity.

Statistical Analysis

A significance level of $P < 0.05$ was used for all analyses. Data are reported as means ± SD unless specified otherwise. Although an a priori sample size was not estimated for this retrospective analysis, the sample size of 29 per group provides greater than 80% power to detect a 20% difference in peak VO_2, assuming an SD similar to that in this study and others.[2–5] Group comparisons were made using unpaired *t*-tests for continuous variables and the Pearson's chi-square test for categorical variables. Comparisons were made for linear exercise response slopes and for measurements at rest, the V_T/V_E inflection point, the ventilatory threshold and peak exercise. Pearson correlations were conducted to evaluate simple associations between variables. To evaluate the relationship between peak VO_2 (dependent variable) and relevant independent variables during exercise, the following were included in a multivariable linear regression model: the independent variable of interest, group as a categorical effect, and an interaction term to determine whether the relationship being tested was similar across groups (variable × group). Independent variables included measurements of pulmonary function, respiratory and limb muscle strength, the ventilatory threshold, and symptom intensity slopes (dyspnea/V_E, dyspnea/VO_2, leg discomfort/VO_2). Forward stepwise multiple regression analysis incorporating group as a categorical effect was carried out with significant independent variables. Analyses were conducted using Systat® 6.1 (Systat Software Inc., San Jose, CA).

Results

Subject characteristics and breast cancer stage are presented in Table 1. There were no significant between-group differences in demographics or anthropometrics. All subjects were aged older than 35 years and had a body mass index (BMI) between 18.5 and 35 kg/m^2, except one underweight (16.1 kg/m^2) cancer patient who had always been underweight and one subject per group with a BMI

Table 1
Subject Characteristics

Characteristic	Breast Cancer ($n = 29$)	Healthy Control ($n = 29$)
Age, yrs	61 ± 12	59 ± 11
Height, cm	162 ± 6	164 ± 4
Weight, kg	73 ± 15	71 ± 12
Weight, % of ideal	116 ± 21	111 ± 20
Body mass index, kg/m^2	27.7 ± 4.9	26.2 ± 4.9
Waist-to-hip ratio	0.82 ± 0.07	0.81 ± 0.07
Skinfold thickness (sum of 5), mm	90 ± 37	96 ± 33
Cancer stage, *n* (%)		
1	14 (48.3)	—
2	5 (17.2)	
3	5 (17.2)	
4	5 (17.2)	
Cancer treatment, *n* (%)		
Surgery	28 (96.6)	—
Radiotherapy	23 (79.3)	
Chemotherapy	10 (34.5)	
Hormonal therapy	18 (62.1)	
Time since last cancer treatment,[a] months	33 ± 39	—
Cigarette smoking history, pack-years	6 ± 11	2 ± 4
Cigarette smoking status, *n* (%)		
Current	1 (3.4)	0 (0)
Never	13 (44.8)	16 (55.2)
Exsmoker	15 (51.7)	13 (44.8)
Habitually active, *n* (%)	15 (51.7)	17 (58.6)
Baseline Dyspnea Index total score (0–12)	8.0 ± 2.8[b]	11.2 ± 1.1
Modified MRC dyspnea scale (0–4)	1.1 ± 1.0[b]	0.3 ± 0.5
Muscle torque (90°/s), Nm		
Elbow extension	18.2 ± 5.8[b]	23.9 ± 4.9
Elbow flexion	19.2 ± 6.6[b]	24.9 ± 4.2
Knee extension	60.5 ± 21.8[b]	78.9 ± 21.8
Knee flexion	41.0 ± 17.6[b]	55.2 ± 15.7

MRC = Medical Research Council.
Values are means ± SD or *n*.
[a]Surgery, radiotherapy, or chemotherapy.
[b]$P < 0.05$, breast cancer versus healthy control group.

between 35 and 40 kg/m^2. Chronic activity-related dyspnea was greater in the cancer group than in controls. Subjects were habitually physically active in 52% and 59% of the cancer and control group, respectively. Smoking history was similar across groups: the majority were nonsmokers or remote exsmokers with only one current smoker in the cancer group.

Cancer treatments varied and included lumpectomy ($n = 9$) or mastectomy ($n = 19$); radiotherapy ($n = 23$); and chemotherapy ($n = 10$) and/or drug therapy with either tamoxifen or anastrozole ($n = 18$; $n = 5$ of these in combination with chemotherapy). The majority received two or more types of treatment (surgery plus chemotherapy and/or radiotherapy), whereas three women had only surgery with hormone drug therapy. The cancer group had no significant abnormalities in serum albumin or electrolyte concentrations. Blood hemoglobin concentration was 136 ± 11 g/L, hematocrit was 0.40 ± 0.03, and resting oxyhemoglobin saturation was 95.6 ± 1.8% in the cancer group.

Pulmonary function measurements were, on average, within normal ranges, but the cancer group had a significantly lower IC, total lung capacity (TLC), D_LCO, maximal midexpiratory flow (FEF_{50}), and MIP compared to controls (Table 2). The lower D_LCO (corrected for hemoglobin) in the cancer group was accompanied by a lower D_LCO relative to alveolar volume (D_LCO/V_A) ($r = 0.750$, $P < 0.0005$): although D_LCO was within normal limits on average in the cancer group, $n = 2$ had a moderate-to-severe reduction (<60% predicted) and $n = 12$ had a mild reduction (60%–80% predicted), in contrast to only $n = 3$ with a mildly reduced D_LCO in the control group. Limb muscle strength was significantly reduced in the cancer group compared to controls (Table 1). Across groups, respiratory muscle strength (MIP and MEP) correlated significantly with leg strength (knee flexion and extension) (all relationships $P < 0.01$).

Table 2
Resting Pulmonary Function

Measurement	Breast Cancer ($n = 29$)	Healthy Control ($n = 29$)
FEV_1, % predicted	107 ± 18	114 ± 15
FEV_1/FVC, %	77 ± 6	79 ± 4
PEF, % predicted	103 ± 24	111 ± 20
FEF_{50}, % predicted	63 ± 22[a]	77 ± 20
IC, % predicted	97 ± 17[a]	108 ± 23
SVC, % predicted	105 ± 15	110 ± 13
FRC, % predicted	102 ± 13	104 ± 19
RV, % predicted	96 ± 13	103 ± 22
TLC, % predicted	100 ± 9[a]	106 ± 10
sRaw, % predicted	146 ± 54	149 ± 65
D_LCO, % predicted	81 ± 21[a]	98 ± 15
D_LCO adjusted for Hb, % predicted	84 ± 21[a]	—
D_LCO/V_A, % predicted	101 ± 20[a]	112 ± 16
V_A, % TLC	85 ± 9	86 ± 8
MIP, cm H_2O (% predicted)	51 ± 20 (82 ± 29)[a]	65 ± 25 (102 ± 38)
MEP, cm H_2O (% predicted)	79 ± 33 (57 ± 24)	93 ± 34 (66 ± 24)

FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; PEF = peak expiratory flow; FEF_{50} = forced expiratory flow at 50% of forced vital capacity; IC = inspiratory capacity; SVC = slow vital capacity; FRC = functional residual capacity; RV = residual volume; TLC = total lung capacity; sRaw = specific airway resistance; D_LCO = diffusing capacity of the lung for carbon monoxide; Hb = hemoglobin; V_A = alveolar volume; MIP = maximal inspiratory mouth pressure; MEP = maximal expiratory mouth pressure.
Values are means ± SD.
[a]$P < 0.05$ cancer versus control group.

Exercise Responses

Peak exercise data are presented in Table 3. Compared with controls, cancer patients had a significantly lower peak VO_2. A ventilatory threshold was identified in all but one subject per group and occurred at a VO_2 of 14.9 ± 2.9 and 18.1 ± 3.5 mL/kg/minute or 58 ± 9 and 65 ± 10% of predicted maximum in the cancer and control groups, respectively ($P < 0.0005$). Twenty-one (72%) cancer subjects

Table 3
Peak Incremental Exercise

Measurement	Breast Cancer	Healthy Control
Reason for stopping exercise, *n* (%)		
Dyspnea	13 (45)	12 (41)
Leg discomfort	8 (28)	5 (17)
Both dyspnea and leg discomfort	1 (7)	3 (10)
Fatigue	5 (17)	1 (3)
Other	1 (3)[a]	8 (28)
Dyspnea, Borg units	4.2 ± 2.3	4.0 ± 1.9
Leg discomfort, Borg units	3.6 ± 2.2	3.3 ± 2.3
VO_2, L/minute	1.55 ± 0.44[a]	2.04 ± 0.59
VO_2, % predicted maximum	83 ± 3[a]	105 ± 4
VO_2, mL/kg/minute	21.4 ± 5.0[a]	29.1 ± 8.6
Heart rate, % predicted maximum	86 ± 10	88 ± 7
RER	1.03 ± 0.11	1.08 ± 0.10
SpO_2, %	93.4 ± 3.5	92.2 ± 3.5
$P_{ET}CO_2$, mm Hg	43.2 ± 5.8	44.4 ± 4.3
V_E, L/minute	45.1 ± 14.1[a]	60.0 ± 16.7
V_E/VCO_2	28.5 ± 4.4	27.7 ± 3.9
V_E, % MVC	57 ± 17	65 ± 16
F_b, breaths/min	31.6 ± 5.4[a]	35.3 ± 6.5
T_I/T_{TOT}	0.46 ± 0.03	0.47 ± 0.02
V_T, L	1.42 ± 0.35[a]	1.70 ± 0.39
V_T/IC, %	72 ± 14	77 ± 12
IC, L	1.97 ± 0.36[a]	2.21 ± 0.35
ΔIC peak rest, L	−0.17 ± 0.26	−0.23 ± 0.30
IRV, L	0.55 ± 0.32	0.51 ± 0.25
EILV, % TLC	89 ± 6	91 ± 5
Expiratory flow limitation, % V_T overlap	12 ± 19	11 ± 23

VO_2 = oxygen uptake; RER = respiratory exchange ratio; SpO_2 = oxygen saturation measured by pulse oximetry; $P_{ET}CO_2$ = partial pressure of end-tidal carbon dioxide; V_E = minute ventilation; MVC = maximum ventilatory capacity estimated as 35 × FEV_1; F_b = breathing frequency; T_I/T_{TOT} = inspiratory time over total breath time (inspiratory duty cycle); V_T = tidal volume; IC = inspiratory capacity; IRV = inspiratory reserve volume; EILV = end-inspiratory lung volume; TLC = total lung capacity.
Values are means ± SD.
[a]$P < 0.05$, cancer versus control group.

and 26 (90%) control subjects met at least one of the following criteria of a maximal response: peak $VO_2 \geq 85\%$ predicted, peak HR > 90% predicted, or respiratory exchange ratio > 1.1.[39] Of those not meeting these criteria, all had an inspiratory reserve volume (IRV) <1L suggestive of a ventilatory constraint. Reasons for stopping exercise were not different between groups with regard to selection frequency of dyspnea, legs, the combination of dyspnea and legs, and fatigue; other reasons were reported by one cancer subject (lightheadedness) and eight controls (panic, too hot, hip/knee/calf pain, dizziness, claustrophobia, dry mouth) (Table 3).

Selected cardiopulmonary exercise responses are shown in Figure 1. Compared with controls, cancer patients reached a lower peak V_E but V_E/VCO_2 relationships were similar: V_E-VCO_2 slopes and intercepts, V_E/VCO_2 at the ventilatory threshold, and the V_E/VCO_2 nadir were not significantly different between groups. The cancer group reached a similar peak HR but had a steeper HR/VO_2 slope ($P < 0.005$) compared with controls. There was no group difference in SpO_2 during exercise.

Breathing pattern and lung volume responses are shown in Figure 2. Peak V_T was significantly lower in the cancer group than in controls. An inflection in the V_T/V_E relationship occurred at a lower V_T (1.33 ± 0.31 vs. 1.61 ± 0.41 L; $P = 0.005$) and at an earlier V_E (32.2 ± 8.4 vs. 41.5 ± 11.2 L/minute; $P < 0.001$) and VO_2 (71 ± 16 vs. $87 \pm 19\%$ predicted maximum; $P = 0.001$) in cancer vs. control subjects; thereafter, increases in V_E were accomplished primarily by increasing breathing frequency (F_b). The diminished V_T response to exercise was driven by reductions in IC (and IRV), thus both groups reached a similar critically reduced IRV at end exercise. The extent of dynamic hyperinflation during exercise (change in IC from rest) was similar across groups. Some degree of expiratory flow limitation was present in four and two subjects at rest and in 10 and six subjects at peak exercise in the cancer and control groups, respectively. Across groups, significant interrelationships were found between MIP % predicted, IC% predicted at rest and during exercise, peak V_T, and peak V_E (all $P < 0.005$).

Exertional dyspnea intensity expressed as a slope against either V_E or VO_2 was greater ($P < 0.05$) in cancer patients than controls (Fig. 3). Slopes of leg discomfort ratings over VO_2 were also greater ($P < 0.05$) in cancer patients than controls (Fig. 3).

An exploratory subgroup analysis within the cancer group showed no significant differences between patients who received chemotherapy ($n = 10$) versus those who did not ($n = 18$) for any of the outcome measures tested, that is, peak VO_2, dyspnea slopes, pulmonary function, and exercise responses.

Correlates of Peak Exercise Capacity

Peak VO_2 % predicted correlated well with slopes of dyspnea/V_E ($P = 0.006$) and dyspnea/VO_2 ($P = 0.011$) but not with leg discomfort/VO_2 ($P = 0.160$). The best physiological correlates of peak VO_2 % predicted were leg strength ($P = 0.001$), VO_2 % predicted at the ventilatory threshold ($P = 0.002$), D_LCO/V_A % predicted ($P = 0.005$), IC % predicted ($P = 0.019$), D_LCO % predicted ($P = 0.027$); there were no significant group effects or group interactions for any of these independent variables. The best combination of physiological variables to explain peak VO_2 % predicted was leg strength, D_LCO/V_A % predicted, IC % predicted, and VO_2 % predicted at the ventilatory threshold ($r^2 = 0.680$). With only resting measurements in the model, the best combination of variables to explain peak VO_2 % predicted was D_LCO/V_A % predicted and IC % predicted ($r^2 = 0.410$). Age, BMI, and cancer stage did not contribute significantly to any relationship.

Discussion

The main findings of this study were that women treated for breast cancer, compared to controls, had 1) increased exertional symptoms and a lower peak VO_2; 2) modest but consistent reductions in lung diffusion but no clear evidence of reduced ventilatory efficiency during exercise; 3) reduced respiratory and peripheral muscle strength and reduced ventilatory thresholds during exercise; and 4) a smaller IC and a shallower breathing pattern during exercise. The results support the hypothesis that dyspnea and exercise intolerance in breast cancer survivors is associated not only with increased ventilatory demand but also with reduced IC, likely secondary to inspiratory muscle weakness.

The cancer and control groups were well matched for age and anthropometrics and reported similar habitual activity levels based on direct questioning. Patients were clinically stable but reported moderate chronic activity-related dyspnea. This was corroborated by greater dyspnea intensity and ~20% lower peak VO_2 during exercise testing. Patients with background cardiorespiratory diseases or other comorbidities that could contribute to exercise intolerance were not included in the study. This allowed an evaluation, in relative isolation, of the respiratory mechanisms of exercise intolerance attributable to the cancer and its treatment.

Spirometry and plethysmographic lung volumes were similar in both groups except for a modestly lower IC and TLC in the cancer group. In accordance

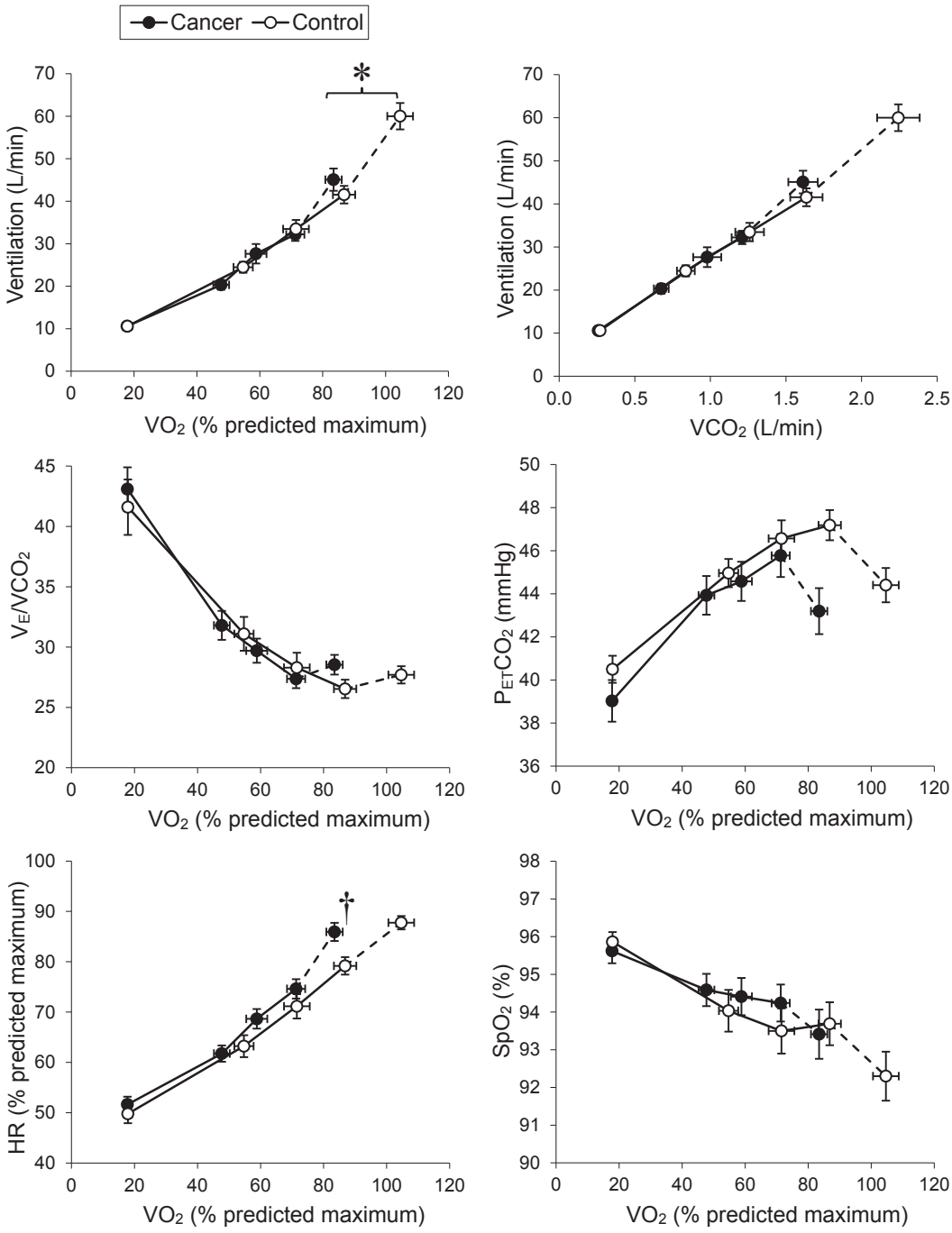

Fig. 1. Selected cardiopulmonary responses to exercise are shown in women with breast cancer and in healthy controls. Data are mean ± SEM values plotted at rest, at each stage of exercise, at the inflection point of tidal volume (V_T) relative to ventilation (V_E), and at peak exercise. *$P < 0.05$ between-group difference in peak VO_2; †$P < 0.05$ between-group difference in HR-VO_2 slopes. HR = heart rate; SEM = standard error of the mean; SpO_2 = oxygen saturation; VCO_2 = carbon dioxide output; V_E/VCO_2 = ventilatory equivalent for carbon dioxide; VO_2 = oxygen uptake.

with previous studies, D_LCO and D_LCO/V_A were reduced in the cancer group, and in the absence of airway obstruction or anemia.[6–8,12–15] This suggests microvascular injury as a consequence of prior radiotherapy or, less likely, chemotherapy. However, the average D_LCO and D_LCO/V_A remained within predicted normal ranges. Patients had no documentation of radiation pneumonitis and no evidence of treatment-related interstitial lung disease or fibrosis on chest radiographs before study entry.

Mild-to-moderate inspiratory and peripheral muscle weakness was present in the cancer group versus controls: both measures of muscle strength were ~20% lower, on average, in the cancer group. The close

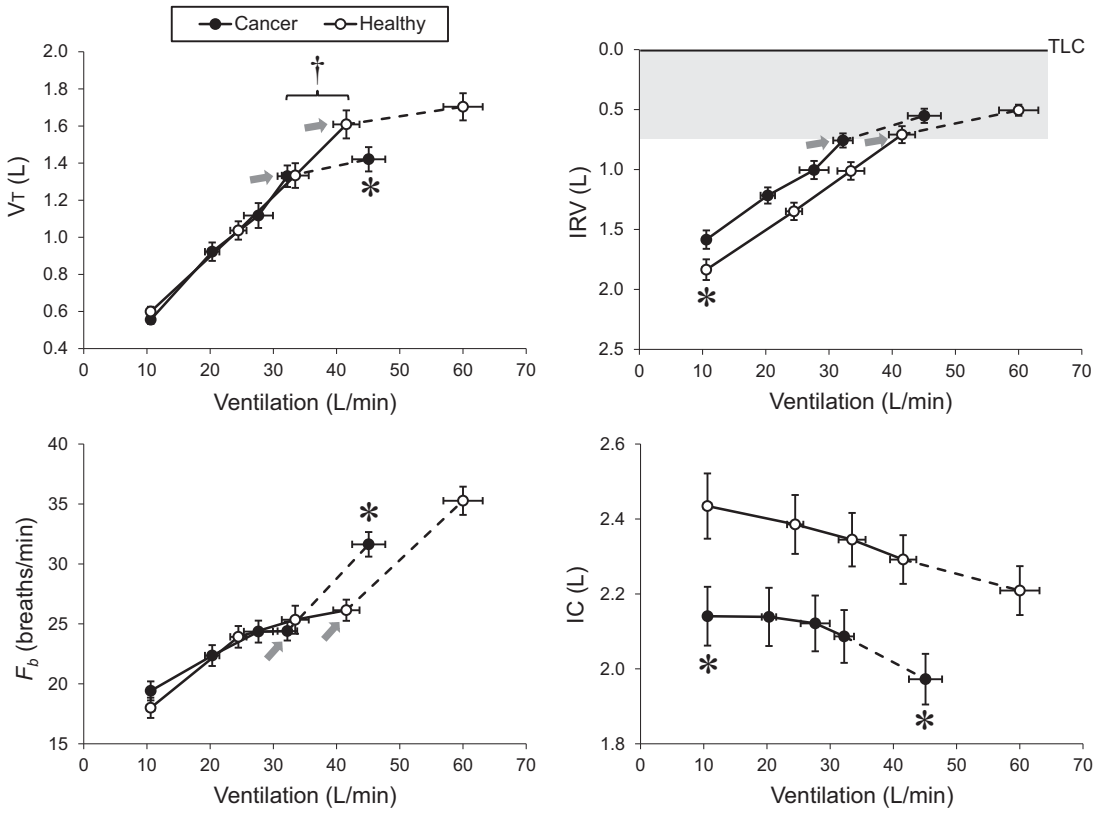

Fig. 2. Breathing pattern and operating lung volume responses to exercise are shown in the cancer and healthy control groups. The inflection point of the relationship between tidal volume (V_T) and ventilation (arrows) occurred at a significantly lower V_T and ventilation ($\dagger P < 0.05$) in the cancer group compared with controls. At this point, inspiratory reserve volume (IRV) was critically reduced (shaded area) and breathing frequency (F_b) accelerated to sustain further increases in ventilation in both groups. There was also a decreased IC at rest and throughout exercise in the cancer group compared with controls. Data are mean ± SEM values plotted at rest, at each stage of exercise, at the inflection point of tidal volume (V_T) relative to ventilation (V_E), and at peak exercise. $*P < 0.05$ between-group difference in the y-axis variable at rest or at peak exercise. IC = inspiratory capacity; SEM = standard error of the mean; TLC = total lung capacity; VC = vital capacity.

correlation between respiratory and peripheral muscle strength across groups points to the likelihood of generalized skeletal muscle weakness in the cancer group. In this context, reduced nutritional status could not be implicated by BMI, skinfold thickness, albumin, electrolyte, or hemoglobin measurements. Additionally, cancer cachexia and chemotherapy-related myopathy or neuropathy were not clinically identified in individual patients. By exclusion, generalized muscle weakness was likely the result of the effects of reduced physical activity and skeletal muscle deconditioning. Collectively, the presence of generalized muscle weakness, a lower ventilatory threshold, higher submaximal HRs, and greater exertional symptoms are all compatible with lower cardiorespiratory fitness and greater deconditioning.

The important role of respiratory factors in contributing to reduced exercise tolerance in the breast cancer group is supported by the associations between peak VO_2 and exertional dyspnea intensity, lung diffusion, IC, and the ventilatory threshold. The question arises: why was dyspnea intensity increased at a given VO_2 and V_E in the cancer group? In general terms, abnormal increases in activity-related dyspnea in the clinical setting can be explained by increased neural respiratory drive (secondary to metabolic and pulmonary gas exchange abnormalities), impaired dynamic respiratory mechanics and muscle function, or any combination of these.[40,41] In the cancer group, ventilatory demand was relatively increased at high exercise intensities, likely reflecting earlier metabolic acidosis due to deconditioning as previously reported.[3,16] Greater ventilation at a lower VO_2, and the associated increase in neural respiratory drive, is likely an important source of earlier onset dyspnea in the cancer group.

The potential contribution of increased ventilation-perfusion inequalities and high physiological dead space to the heightened ventilatory response was considered, particularly in the setting of a relative, albeit modest, D_LCO reduction in the cancer group. However, V_E/VCO_2 before the ventilatory threshold and at its nadir—an index of ventilatory efficiency and an indirect measure of physiological dead

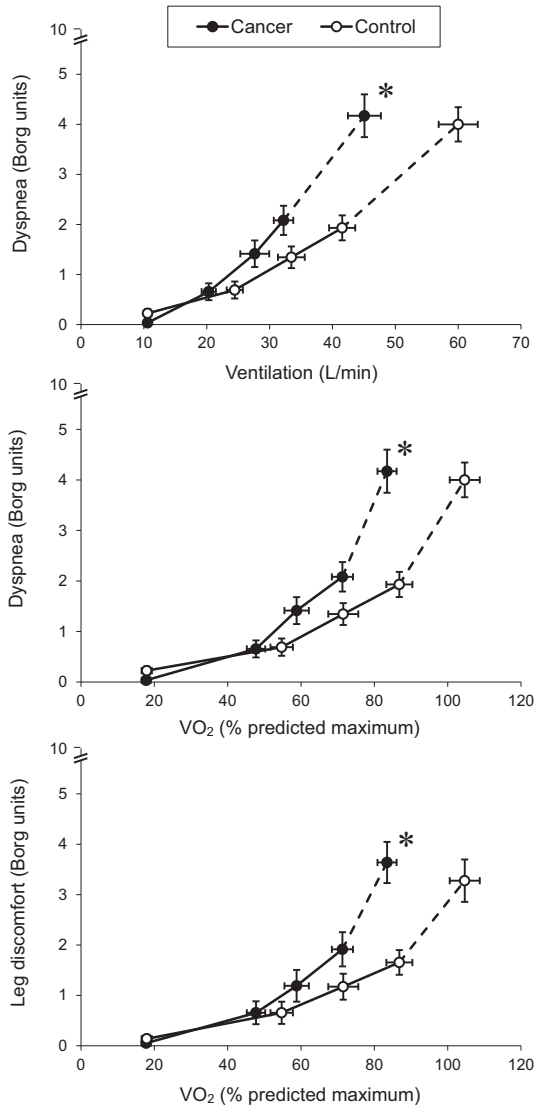

Fig. 3. Exertional symptom intensity is shown in the cancer and healthy control groups. Data are mean ± SEM values plotted at rest, at each stage of exercise, at the inflection point of tidal volume (V_T) relative to ventilation (V_E), and at peak exercise. *$P < 0.05$ between-group difference in slopes. SEM = standard error of the mean.

space—and other measures of pulmonary gas exchange were similar in both groups and cannot easily be implicated in increasing neural respiratory drive and associated dyspnea.

We found no evidence of significant impairment of airway function or pulmonary gas trapping, and no increase in estimates of expiratory flow limitation during exercise in the cancer group. It follows that in the absence of increased mechanical loading, inspiratory muscle weakness provides a plausible explanation for increased dyspnea intensity at any given ventilation during exercise. The contention that significant dynamic inspiratory muscle weakness existed in the cancer group is bolstered by the fact that lower IC, MIP, peak V_T, and peak V_E were statistically interrelated. A lower IC in the absence of lung hyperinflation reflects a reduced ability to inspire to TLC because of muscle weakness. In the cancer group, IC (and IRV) was lower throughout exercise and consequently, the V_T/V_E inflection occurred at a ~20% lower VO_2 and V_E. The inability to fully expand V_T at higher exercise intensities meant that patients relied more on increasing F_b to increase V_E in pace with metabolic demand. In the setting of inspiratory muscle weakness, respiratory motor command output, central corollary discharge, and contractile muscular effort must increase to maintain adequate force generation. These neurophysiological perturbations, in turn, are linked to perceived respiratory discomfort at a lower ventilation than in healthy controls.[40,41]

Our results indicate that peripheral muscle weakness also played an important role in exercise intolerance in the cancer group: measures of leg strength correlated well with peak VO_2. Greater perceived leg discomfort at any given VO_2 in the cancer group may reflect awareness of the increased motor command output required to drive the weakened locomotor muscles. Thus, in accordance with current theoretical constructs, greater perceived leg and respiratory discomfort during exercise may share common neurophysiological origins.[40,41]

Limitations

Our results may not be generalizable to all patients with breast cancer. However, to minimize confounding by clinical heterogeneity, our selection criteria specified presence of clinical stability, absence of radiological and spirometric abnormalities, evidence of adverse treatment effects, or significant comorbidities which may be implicated in dyspnea causation and exercise intolerance. Because of the relatively small sample size and heterogeneity of cancer stage and treatment, we could not adequately perform subgroup analyses or determine the precise origins of the physiological abnormalities we uncovered. We used patient recall to evaluate habitual activity levels rather than objective quantification. Because our focus was on physiological factors in exercise intolerance, we were unable to explore the biological basis of skeletal muscle weakness. Finally, the precise etiology of the reduced D_LCO could not be determined: computed tomography of the lungs may have revealed structural changes of interstitial disease or fibrosis not visualized with plain radiography.

Conclusions

Women treated for breast cancer reported greater chronic activity-related dyspnea and had objectively

diminished exercise capacity compared with healthy controls. Women with cancer showed evidence of deconditioning with lower ventilatory thresholds during standardized exercise testing, which likely contributed to earlier onset of dyspnea. They also had general skeletal muscle weakness compared with controls. In the cancer group, reduced IC and static inspiratory muscle strength, a more rapid and shallow breathing pattern, and higher dyspnea intensity ratings during exercise were consistent with the presence of significant dynamic inspiratory muscle weakness. The clinical implication of this study is that potentially reversible factors such as inspiratory muscle weakness can be identified by simple tests in individual patients with breast cancer.

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